REMARKS

Claims 1-55 were pending. Claims 1-3 and 5-19 have been cancelled. Claims 30, 32, 33, 38, 48 and 55 were amended. Therefore, claims 4, and 20-55 are currently pending.

No new matter has been added. Claims 30, 32, 48, and 55 have been amended to clarify the invention. Support for the amendment to claims 30 and 32 can be found, for example, in the specification as originally filed, at least at page 3, line 26. Support for the amendment to claim 55 can be found, for example, at least in claim 55 as originally filed, and in claim 55 of U.S.S.N. 60/239,541, incorporated into the instant specification by reference at page 1, lines 7-9. Claims 33 and 38 have been amended to correct grammatical errors.

Rejection of Claims 4, and 20-55 under 35 U.S.C. § 112, second paragraph

Claims 4, and 20-55 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In particular, claims 30 and 32 were "rejected over the recitation of the phrase, 'other disorder.'" It is respectfully submitted that this rejection no longer pertains to the claims as currently amended.

Claim 48 was rejected because the Examiner found that the phrase "searchable" rendered the claim indefinite. Applicants respectfully submit that this rejection no longer applies to the claims as currently amended.

The Examiner rejected claim 55 as being "vague and indefinite" as being dependent on a non-elected claim. It is respectfully submitted that this rejection no longer pertains to the claim as currently amended.

In addition, the Examiner found claims 4 and 20-55 to be "vague and indefinite" because of the "recitation of the phrase, 'small molecules.'" Applicants respectfully disagree. The term "small molecules" is defined in the specification, for example, at least at page 6, lines 1-16. One of ordinary skill in the art would be able to use the definition in the specification to be reasonably apprised of the scope of the invention.

The Examiner also rejected claims 21, 33, and 38 "over the recitation of the phrase, 'cellular compartment is a cell(s).'" Applicants respectfully submit that the term "cellular compartment" is defined in the specification for example, at least at, page 5, lines 21-25, to include both the entire cell, in certain embodiments, and in others, particular organelles. Applicants submit that one of ordinary skill in the art would have

been able to use the teachings in the specification to determine the metes and bounds of the claims.

Therefore, Applicants request that these rejections of claims 4, and 20-55 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejection of Claims 20-26 under 35 U.S.C. § 112, first paragraph

Applicants gratefully acknowledge the Examiner's finding that the specification is enabling for methods of identifying human tumors.

Claims 20-26 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In particular, the Examiner states that "the specification...does not reasonably provide enablement for identifying any disease in any living organism."

Applicants respectfully disagree. Applicants' invention is based, at least in part, on the discovery that disease states alter the concentrations of particular small molecules within cells or other cellular compartments of a subject. For example, through comparison of subjects suffering from the same disease state, Applicants found that they were able to determine which small molecule concentrations were characteristic of a particular disease state.

The claims do not suppose an *a priori* knowledge of molecules relevant to a particular disease state. Rather, the claimed methods are directed to a method for identifying disease related small molecules by comparing the small molecule profile of a diseased cell to that of a healthy cell. An ordinarily skilled artisan would be able to use the methods taught by Applicants' specification and apply the methods to any given disease, by the comparison of small molecule profiles from individuals suffering the disease. Therefore, Applicants respectfully submit that the specification does enable one of ordinary skill in the art to make and use the claimed invention.

Rejection of Claims 4, 20, 21, 23-33, 35-38, 40-50, 52 and 55 under 35 U.S.C. § 102(e)

Claims 4, 20, 21, 23-33, 35-38, 40-50, 52 and 55 are rejected under 35 U.S.C. § 102(e), as being anticipated by Kaser *et al.* (U.S. Patent No. 6,168,933 B1). Applicants respectfully disagree.

Kaser *et al.* is directed to a mammalian nucleic acid molecule (1865 nucleotides), which encodes a phospholipid transfer protein (291 amino acids). Kaser *et al.* also provides for the use of the nucleic acid molecule for the characterization, diagnosis,

evaluation, treatment or prevention of conditions, diseases, and disorders associated with the gene expression. Kaser *et al.* does not anticipate methods of using the metabolome nor any methods involving small molecule profiles, as claimed by Applicants.

Claim 4 is directed to a method for metabolomically monitoring the effectiveness of a therapeutic agent in clinical trials. The method includes obtaining a small molecule profile from a subject in a clinical trial being treated with a therapeutic agent; and monitoring the changes in the small molecule profile of the subject as an indication of the effectiveness of the therapeutic agent in the subject.

Claim 20 is directed to a method for identifying disease relevant small molecules. The method includes obtaining a small molecule profile of a diseased cellular compartment, and comparing the small molecule profile of the diseased cell to a standard small molecule profile. Claims 21, and 23-26 are dependent claims of claim 20 and contain all of its limitations.

Claim 27 is directed to a method for identifying small molecules affected by an agent. The method includes obtaining a small molecule profile of said cellular compartment treated with an agent, and comparing the small molecule profile to a standard small molecule profile. Claims 28-33, 35 and 36 are dependent claims of claim 27 and contain all of its limitations.

Claim 37 is directed to a method for identifying small molecules regulated, modulated, or associated with a gene. The method includes obtaining a small molecule profile of a cellular compartment from a genetically modified source; and comparing the small molecule profile to a standard small molecule profile. Claims 38, and 40-43 are dependent claims of claim 37 and contain all of its limitations.

Claim 44 is directed to a method for identifying potential cell drug targets. The method includes contacting a labeled disease relevant small molecule with cellular components, and identifying interactions between said cell components and the labeled disease-relevant small molecule. Claims 45-47 are dependent claims of claim 44, and contain all of its limitations.

Claim 48 is directed to a library of small molecules of a cellular compartment of a cell comprising an array of samples of small molecules from a cellular compartment. Claims 49, 50 and 52 are dependent claims of claim 48, and contain all of its limitations.

Claim 55 is directed to a pharmaceutical composition comprising a small molecule identified by the methods of the invention.

Applicants' claimed methods are based, at least in part, on the comparison of small molecule profiles. Applicants' small molecule profiles are defined in Applicants' specification at page 6, line 25-27, as an "inventory of small molecules in tangible form

within a targeted cell, tissue, organ, organism, or any derivative fraction thereof." On page 6, lines 1-3, Applicants define small molecules as "organic and inorganic molecules which are present in the cell, cellular compartment, or organelle. The term does not include large macromolecules." Applicants' claimed methods do not include the analysis of large macromolecules such as the nucleic acids and proteins described by Kaser *et al.*

Kaser *et al.* fails to teach or suggest a method for metabolomically monitoring the effectiveness of a therapeutic agent in clinical trials, as claimed by Applicants. For example, Kaser *et al.* neither teaches nor suggests using small molecule profiles as claimed by Applicants. Kaser *et al.*'s methods involve macromolecules such as DNA, RNA, PNA, proteins, etc, which are not "small molecules" as defined by Applicants. Furthermore, there is no teaching or suggestion in Kaser *et al.* of monitoring changes in a subject's small molecules while under going treatment.

Kaser *et al.* fails to teach or suggest a method for identifying disease relevant small molecules. As discussed above, Kaser *et al.* fails to teach or suggest methods involving small molecule profiles, as defined by Applicants. Furthermore, Kaser *et al.* does not teach or suggest the comparison of small molecule profiles to determine disease relevant small molecules. Applicants' definition of "small molecule" and "small molecule profile" do not include the methods described involving proteins and large nucleic acids, described by Kaser *et al.*

Kaser *et al.* fails to teach or suggest a method for identifying small molecules affected by an agent. Kaser *et al.* fails to teach or suggest methods involving the determination or use of small molecule profiles. Kaser *et al.* does not teach or suggest the comparison of small molecule profiles, as defined by Applicants, to determine small molecules affected by the administration of an agent. Applicants' definition of "small molecule" and "small molecule profile" do not include the methods described involving proteins and large nucleic acids, described by Kaser *et al.*

Kaser *et al.* fails to teach or suggest a method for identifying small molecules regulated, modulated, or associated with a gene. Kaser *et al.* fails to teach or suggest methods involving the determination or use of small molecule profiles, as claimed by Applicants. Kaser *et al.* does not teach or suggest obtaining a small molecule profile of a cellular compartment from a genetically modified source; and comparing the small molecule profile to a standard small molecule profile. Applicants' definition of "small molecule" and "small molecule profile" do not include the methods described involving proteins and large nucleic acids, described by Kaser *et al.*

Kaser *et al.* fails to teach or suggest a method for identifying potential cell drug targets, by contacting a labeled disease relevant small molecule with cellular components,

and identifying interactions between said cell components and the labeled disease-relevant small molecule. Applicants' claim methods for determining targets which bind to a particular disease relevant small molecule. Applicants do not claim methods involving affinity screens of nucleic acids as described in Kaser *et al.*

Kaser *et al.* fails to teach or suggest a library of small molecules of a cellular compartment of a cell comprising a searchable array of samples of small molecules from a cellular compartment. In contrast, at column 15, line 45 to column 16, line 24, Kaser *et al.* describe libraries as comprising macromolecules such as "DNA and RNA molecules, peptides, PNAs, proteins, and the like." Applicants' claimed small molecule libraries do not include large macromolecules, as described by Kaser *et al.*

Kaser *et al.* also fails to teach or suggest pharmaceutical compositions comprising a small molecule identified by the methods of the invention, as claimed by Applicants. At column 16, lines 25-49, Kaser *et al.* discusses pharmaceutical compositions generally as background, and describes principles widely known in the art, such as how to determine an effective dose. Kaser *et al.* fails to anticipate pharmaceutical compositions comprising small molecules identified by the methods of Applicants invention.

Therefore, Applicants respectfully request that this rejection of claims 4, 20, 21, 23-33, 35-38, 40-50, 52 and 55 under 35 U.S.C. § 102(e), be withdrawn.

Rejection of Claims 20, 22, 48, 51 and 54 under 35 U.S.C. § 102(e)

Claims 20, 22, 48, 51 and 54 are rejected under 35 U.S.C. § 102(e) as being anticipated by Polyak *et al.* (U.S. Patent No. 6,344,322 B1).

Polyak *et al.* is directed to methods of detecting a tumor by determining the presence of a single basepair mutation in the mitochondrial genome from a cell sample of a patient. Polyak *et al.* does not teach or suggest methods of using of the metabolome nor any methods involving small molecule profiles, as claimed by Applicants. The mitochondrial DNA described in Polyak *et al.* are not a small molecules as defined by Applicants.

As described above, claims 20 and 22 are directed to methods for identifying disease relevant small molecules, by obtaining a small molecule profile of a diseased cellular compartment, and comparing the small molecule profile of the diseased cell to a standard small molecule profile.

As described above, claims 48 and 51 are directed to libraries of small molecules of a cellular compartment of a cell comprising a searchable array of samples of small molecules from a cellular compartment.

Claim 54 is directed to a method for determining whether small molecule profiles are from the same individual. The method includes obtaining one or more samples from an individual; determining the small molecule profiles of said samples; obtaining a tissue sample from an unknown source; determining the small molecule profile of the unknown source; and comparing the small molecule profiles.

Polyak *et al.* fails to anticipate methods for identifying disease relevant small molecules, by obtaining a small molecule profile of a diseased cellular compartment, and comparing the small molecule profile of the diseased cell to a standard small molecule profile, as claimed by Applicants. Polyak *et al.* fails to anticipate methods involving small molecule profiles, as claimed by Applicant. Applicants' do not claim methods involving mitochondrial nucleic acids as described in Polyak *et al.* Therefore, the methods described by Polyak *et al.* fail to anticipate the present invention.

As described above, Applicants claim a library of small molecules. Polyak *et al.* do not teach or suggest small molecule libraries as defined by Applicants. Applicants' small molecule libraries do not include DNA sequencing reactions separated on a polyacrylamide gel, as described by Polyak *et al.* The results of these sequencing reactions are macromolecular and are not small molecules as defined by Applicants.

Furthermore, Polyak *et al.* also fails to teach or suggest a method for determining whether small molecule profiles are from the same individual, as claimed by Applicants. Although Polyak *et al.* teach a method for identifying DNA molecules, this method is based on genetic sequencing of macromolecules, rather than the comparison of small molecule profiles which do not include large polynucleotides, like DNA. Applicants' small molecule profiles are based on small molecules found within a particular cellular compartment, rather than the macromolecular DNA described in Polyak *et al.* Therefore, Polyak *et al.* fails to teach or suggest methods for determining whether small molecule profiles are from the same individual.

Therefore, Applicants respectfully request that this rejection of claims 20, 22, 48 and 51 under 35 U.S.C. § 102(e) be withdrawn.

Rejection of Claims 48 and 53 under 35 U.S.C. § 102(e)

Claims 48 and 53 are rejected under 35 U.S.C. § 102(e) as being anticipated by Ward *et al.* (U.S. Patent No. 5,541,310).

Ward *et al.* is directed toward herbicide resistant plants. Ward *et al.* describes the isolation of genes encoding imidazoleglycerol phosphate dehydratase (IGPD) of plants, and the use of the genes, and altered genes, to render plants resistant to certain herbicides, which target that enzyme.

As described above, claims 48 and 53 are directed to libraries of small molecules of a cellular compartment of a cell comprising a searchable array of samples of small molecules from a cellular compartment.

Although the Examiner states that Ward *et al.* "teach[es] a library of small molecules of a cellular compartment of a cell comprising a searchable array of samples of small molecules isolated from a cellular compartment of a chloroplast." The small molecule libraries claimed by Applicants do not include cDNA macromolecules as described in Ward *et al.* Therefore, Applicants respectfully request that this rejection of the claims 48 and 53 under 35 U.S.C. § 102(e), be withdrawn.

Rejection of Claims 4, 20-21, 23-50, 52 and 55 under 35 U.S.C. § 103(a)

Claims 4, 20-21, 23-50, 52, and 55 are rejected under 35 U.S.C. § 103(a) over Kaser *et al.* in view of Polyak *et al.*

As described above, claim 4 is directed to a method for metabolomically monitoring the effectiveness of a therapeutic agent in clinical trials using small molecule profiles. Claims 20, 21, and 23-26 are directed to methods for identifying disease relevant small molecules using small molecule profiles. Claims 27-36 are directed to methods for identifying small molecules affected by an agent using small molecule profiles. Claims 37-43 are directed to methods for identifying small molecules regulated, modulated, or associated with a gene, using small molecule profiles. Claims 44-47 are directed to a method for identifying potential cell drug targets. Claims 48-50, and 52 are directed to libraries of small molecules of a cellular compartment of a cell. Claim 55 is a dependent claim directed to pharmaceutical compositions comprising small molecules identified by the methods of the invention.

As described above, Kaser *et al.* fails to teach or suggest a method for metabolomically monitoring the effectiveness of a therapeutic agent in clinical trials, methods for identifying disease relevant small molecules, methods for identifying small molecules affected by an agent, or methods for identifying small molecules regulated, modulated, or associated with a gene, as claimed by Applicants. Polyak *et al.* fails to overcome the deficiencies of Kaser *et al.* Like Kaser *et al.*, Polyak *et al.* fails to teach or suggest methods involving small molecules and small molecule profiles. One of ordinary skill in the art would have not found the claimed invention obvious in light of Kaser *et al.* in view of Polyak *et al.* because neither of the references teach or suggest methods of using small molecule profiles as claimed by Applicants.

As discussed above, Kaser *et al.* fails to teach or suggest a method for identifying potential cell drug targets. Although Kaser *et al.* describe the use of a nucleic acid

macromolecule for use in an affinity screen, it does not teach or suggest a method for identifying potential cell drug targets using a labeled small molecule, as claimed by Applicants. Polyak *et al.* fails to over come the deficiencies of Kaser *et al.* Like the primary reference, Polyak *et al.* neither teaches or suggests a method for identifying potential cell drug targets using a labeled small molecule. Therefore, an ordinarily skilled artisan would not have been motivated to identify potential cell drug targets using the claimed methods based on Kaser *et al.* in view of Polyak *et al.*

Kaser *et al.* fails to teach or suggest a library of small molecules of a cellular compartment of a cell comprising a searchable array of samples of small molecules from a cellular compartment. Polyak *et al.* does not overcome this deficiency of the primary reference. Like Kaser *et al.*, Polyak *et al.* fails to teach or suggest a library of small molecules, as claimed by Applicant. An ordinarily skilled artisan would not have been motivated to make a library of small molecules as claimed by Applicants based on the teachings of Kaser *et al.*, alone or in combination with Polyak *et al.*, because neither of the two references teach small molecule libraries.

Neither Kaser *et al.* nor Polyak *et al.*, alone or in combination, teach or suggest the methods of the invention using small molecule profiles, as discussed above. An ordinarily skilled artisan, based on the teachings of Kaser *et al.*, in view of Polyak *et al.*, would not be motivated to make the pharmaceutical compositions of the invention because neither Kaser *et al.* nor Polyak *et al.*, teach or suggest methods of identifying small molecules and using these small molecules in pharmaceutical compositions, as claimed by Applicants.

Therefore, Applicants respectfully request that this rejection of claims 4, 20-21, 23-50, 52, and 55 under 35 U.S.C. § 103(a) be withdrawn.

SUMMARY

Cancellation of and/or amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The cancellation of the claims is being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. The amendments made to the claims are not related to any issues of patentability.

In view of the above remarks and amendments, it is believed that this application is in condition for allowance. If a telephone conversation with Applicant's Attorney

would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Date: November 15, 2002

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VERSION OF CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

30. [Amended] The method of claim 29, wherein said therapeutic agent is a therapeutic agent used for the treatment of a metabolic, immunological, neurological, oncological, cardiovascular, or viral~~, or other~~ disorder.

32. [Amended] The method of claim 31, wherein said patient is suffering from a metabolic, immunological, neurological, oncological, cardiovascular, or viral~~, or other~~ disorder.

33. [Amended] The method of claim 27, wherein said cellular compartment is a cell~~s~~.

38. [Amended] The method of claim 37, wherein said cellular compartment is a cell~~s~~.

48. [Amended] A library of small molecules of a cellular compartment of a cell comprising an ~~searchable~~ array of samples of small molecules from a cellular compartment of a cell.

55. [Amended] A pharmaceutical composition comprising a small molecule identified by the method of any one of claims 20, 27, 37, or 44~~1~~.